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Ventilatory and chronotropic incompetence during incremental and constant load exercise in end-stage renal disease: a comparative physiology study

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Abstract

Background: Maximal oxygen uptake is impaired in end-stage renal disease (ESRD), reducing quality of life and longevity. Whilst determinants of maximal exercise intolerance are well defined, little is known of limitation during sub-maximal constant load exercise. By comparing individuals with ESRD and healthy controls, the aim of this exploratory study was to characterise mechanisms of exercise intolerance in ESRD participants by assessing cardiopulmonary physiology at rest and during exercise.

Methods: Resting spirometry and echocardiography were performed in 20 dialysis-dependent ESRD participants (age: 59±12; 14 male) and 20 healthy age and gender matched controls. Exercise tolerance was assessed with ventilatory gas exchange and central hemodynamics during a maximal cardiopulmonary exercise test (CPEX) and 30 minutes of sub-maximal constant load exercise (CLEX).

Results: Left ventricular mass (292±102 *vs.* 185±83 g; p = 0.01) and filling pressure (E/e': 6.48±3.57 *vs.* 12.09±6.50 m/s; p = 0.02) were higher in ESRD participants; forced vital capacity (3.44 ± 1 *vs.* 4.29 ± 0.95 L/min; p = 0.03) and peak VO_2 (13.3±2.7 *vs.* 24.6±7.3 $ml.kg^{-1}.min^{-1}$; p < 0.001) were lower. During CLEX, the relative increase in (a-v) O_2 difference (13 ± 18 *vs.* 74 ± 18%) and heart rate (32±18 *vs.* 75±29%) were less in ESRD participants despite exercise being performed at a higher percentage of maximum VE (48±3 *vs* 39±3%) and HR (82±2 *vs.* 64±2%).

Conclusion: Ventilatory and chronotropic incompetence contribute to exercise intolerance in individuals with ESRD. Both are potential targets for medical and lifestyle interventions.

Key words: NICOM, non-invasive cardiac output monitor; VE, minute ventilation; (a-v) O_2 difference, arterial-venous O_2 difference; CPEX, cardiopulmonary exercise test; CLEX, constant load exercise.

Introduction

Compared to the general population, maximal oxygen uptake (VO_2 peak) is reduced by as much as 50% in end-stage renal disease (ESRD) (1). This exercise intolerance, indicating subclinical and pathological cardiopulmonary impairment, negatively affects activities of daily living and contributes to increased all-cause mortality (1). Our understanding of exercise intolerance in ESRD comes primarily from studies performed with maximal cardiopulmonary exercise testing (CPEX) (2, 3). Whilst maximal exercise testing provides useful information, limitations to activities of daily living may be better understood by observing the physiological response to sustained sub-maximal exercise. This kind of exercise more accurately reflects guidelines for physical activity and health, and many common recreational, leisure and domestic activities such as housework and walking. No study to date has comprehensively evaluated the physiological response to sustained, sub-maximal exercise in people with ESRD. Such studies may help identify additional mechanisms of exercise intolerance in ESRD and inform interventions to attenuate their effects.

In a healthy cardiovascular system, exercise is accompanied by a sympathetically driven increase in ventilation and heart rate, facilitating greater O_2/CO_2 exchange and cardiac output. Combined vasodilation to active tissue (cardiac, pulmonary, cerebral and skeletal muscle) and vasoconstriction to non-active tissue, aids venous return, further augmenting cardiac output via increased left ventricular filling pressures (4). This combined response facilitates oxygen delivery during exercise, enabling mechanical work via aerobic means (5). In people with ESRD, limitations to cardiac output and ventilatory and cellular gas exchange include, but are not limited to, cardiomyopathy, anaemia, systemic inflammation, pulmonary/vascular hypertension, hypervolemia, and electrolyte imbalances (6). The effects of this pathology are evident during the assessment of maximal exercise capacity. However, comprehensive investigation of cardiovascular, metabolic and ventilatory function during exercise has not been undertaken in individuals with ESRD, particularly in the context of sustained constant load exercise (CLEX). In the few available studies comparing healthy controls with small ESRD cohorts, impaired oxygen uptake (VO_2), heart rate, catecholamine sensitivity and glucose metabolism have been reported during sub-maximal exercise (7, 8).

Cardio-pulmonary exercise testing can identify multi-system physiological limitation and, as such, is an important diagnostic and prognostic tool in many pathologies. In ESRD, assessment of oxygen uptake at peak exercise and at the ventilatory anaerobic threshold is predictive of survival (2). However, maximal exercise performance is often symptom limited and hindered by patient motivation (9). Alternatively, sub-maximal exercise testing may provide unique insights into exercise intolerance in ESRD. The intensity and sustained nature of this exercise better represents many activities of daily living and is less dependent on motivation. Sub-maximal constant load exercise may aid our understanding of physiological limitation in ESRD, previously not identified by maximal testing.

By studying the exercise response during sub-maximal constant load and maximal exercise in both healthy individuals and those with ESRD, the aim of this comparative physiology study was to explore key limitations and mechanisms of exercise intolerance in ESRD patients undergoing regular haemodialysis.

Methods

Informed consent was obtained from all participants and the study was approved by the U.K. Health Research Ethics Committee (17/LO/0368) and registered with Clinicaltrials.gov (NCT03064555). All procedures were conducted in accordance with the Declaration of Helsinki.

Study procedures

Untrained ESRD patients undergoing regular haemodialysis were recruited from University Hospital Coventry and Warwickshire NHS Trust. Simultaneously, age and gender matched healthy controls were recruited from a Coventry University register of trial volunteers. Participants from both groups underwent; 1) resting echocardiography, spirometry and brachial artery oscillometry; 2) a maximal cardiopulmonary exercise test (CPEX); and 3) a sub-maximal constant load exercise test (CLEX). To reduce the potential effects of fluid overload and hemodynamic changes resulting from hemodialysis treatment in the ESRD participants, testing was scheduled for the first non-dialysis day, 12 hours after the previous treatment. Seven days separated CPEX and CLEX testing to reduce the effects of cumulative fatigue on

performance. Measures during CPEX and CLEX included ventilatory gas exchange, heart rate (HR) and blood pressure (BP). Additionally, data on central hemodynamics (stroke volume, cardiac output, total peripheral resistance, mean arterial pressure) were collected during CLEX.

Participants

Untrained adults with ESRD, able to perform CPEX and CLEX, undergoing three times weekly hemodialysis treatment for greater than three months, were invited to take part. Exclusion criteria included evidence of clinically significant valvular insufficiency or dysrhythmia, intra-dialytic blood pressure >180 systolic or >95 diastolic, >3 litres fluid accumulation between hemodialysis sessions, hemoglobin < 9.0 g/dL, ischemic cardiac event (<1 month), and planned kidney transplant during the study.

Moderately active (<150 minutes moderate intensity exercise weekly) age and gender matched healthy individuals were eligible for the comparative control group. Exclusion criteria included disease or comorbidity which would prevent full participation in exercise testing or likely elicit an abnormal cardiorespiratory response to exercise.

Echocardiogram

Resting transthoracic echocardiography images were acquired and analyzed (Vivid IQ, Echo-pack version 7.0, GE Medical Systems) by a clinical sonographer prior to CPEX testing, abiding by American Society of Echocardiography guidelines (10). Left ventricular (LV) volumetric parameters were assessed in 2-D and calculated using the Simpson's bi-plane method. Left ventricular mass was calculated at the end of diastole using the 2-D truncated ellipsoid technique. In the apical four-chamber view, pulsed wave Doppler assessed the ratio of early to late mitral inflow velocity (E/a) and E-wave deceleration time. Tissue Doppler imaging was used to quantify peak septal and lateral mitral annuli velocities. Subsequently, the ratio of peak early mitral inflow velocity to mean peak early annuli velocity (E/e') was reported as a surrogate of LV filling pressure.

Spirometry

Resting respiratory function was assessed with spirometry. Participants were asked to breathe normally through a respiratory flow sensor (Ergospirometer, Ergostik, Geratherm Respiratory, Bad Kissingen, Germany). After assessment of tidal flow, each participant performed one maximal inhalation and exhalation. On verification of quality, data were analyzed to provide outputs of forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and the FEV_1/FVC ratio.

Brachial artery oscillometry

To determine arterial stiffness, brachial artery oscillometry (Mobil-O-Graph 24h PWA Monitor, I.E.M. GmbH, Stolberg, Germany) was performed. A cuff was automatically inflated and deflated around the participants' upper (non-fistula) arm, and pulse wave velocity and augmentation index were subsequently calculated.

Noninvasive cardiac output monitor

Throughout CLEX, noninvasive cardiac output monitor (NICOM) bioreactance (Cheetah Medical, Wilmington, Delaware, USA) was used to evaluate central hemodynamics. Four dual sensor electrodes, placed superior to the iliac crest and scapula, measured the relative phase shift of oscillating current traversing the thorax. Each electrode emitted a high-frequency current, averaged after digital processing for 30 seconds. The signal processing unit determines the relative phase shift (Δφ) between the input signal, relative to the output signal. Δφ was calculated relative to changes in blood flow through the aorta, allowing estimation of stroke volume with the equation: $SV = C \cdot VET \cdot d\varphi/dt_{max}$. C is a constant of proportionality and VET is ventricular ejection time determined with ECG as the time between aortic valve opening and closure. $d\varphi/dt_{max}$ indicates the relative bioreactance phase shift from the injected and returning current after traversing the thorax. Cardiac output (CO) was subsequently calculated as the product of stroke volume (SV) and heart rate (HR). In previous studies, NICOM demonstrated good test-retest reliability and validity (11, 12).

Cardiopulmonary exercise test

Cardiopulmonary exercise testing was conducted using an electronically braked cycle ergometer (Ergoline, Love medical, Manchester) with a ramped protocol until exhaustion (13). Sensations associated with the test (e.g. leg fatigue, breathlessness) were explained to participants to limit premature test termination. Participants rested for three minutes to acquire baseline O_2 saturation, blood pressure and HR, then continued with three minutes unloaded cycling at 50rpm. Workload was then increased (5-20 W/min) until exhaustion, with starting load was determined by physical activity history. Electrocardiogram was recorded throughout and BP at two-minute intervals. VO_2 peak was identified as the mean O_2 uptake during the final 20 seconds of exercise. Oxygen uptake at the anaerobic threshold (VO_2AT) was derived via the V-Slope method in conjunction with ventilatory equivalents (13). Predicted VO_2 peak was determined via the Wasserman and Hansen equation (14). The oxygen uptake efficiency slope (OUES), was calculated as the slope of the regression line between VO_2 and the logarithmic transformation of VE, from rest to VO_2 peak.

Constant load exercise test (CLEX)

Constant load exercise was performed on an electronically braked cycle ergometer (lower body bi-directional ergometer, Hudson Fitness, Dallas, Texas) in the semi-recumbent position. Cardiovascular hemodynamics and ventilatory gas exchange were monitored throughout. Participants started with a five-minute warm-up, after which exercise commenced at a workload (watts) equivalent to 90% VO_2AT, determined from CPEX, for a duration of 30 minutes. Calculation of systemic arterial venous O_2 difference was performed indirectly with the Fick equation (VO_2 = CO x [Ca-Cv]; rearranged to: VO_2/CO= [Ca-Cv]), where Ca denotes arterial O_2 content, and Cv denotes venous O_2 content. On completion of the protocol, all participants underwent an unloaded three-minute cool down period at 50 rpm. An additional two-minute resting period was monitored.

Statistical analysis

Due to the exploratory nature of the study, an *a priori* power calculation was not performed. Data were analyzed with the statistical software package SPSS (Version 21, SPSS Inc., Chicago, IL, USA). Baseline echocardiogram, brachial artery oscillometry, spirometry and CPEX

variables were analyzed between groups using an independent samples t-test for each variable. The analysis of gas exchange and cardiovascular responses during CLEX was carried out using a two-way between subjects general linear model to identify differences between groups. Where appropriate, post-hoc analysis identified significance between measurements at each time point between groups. All data were expressed as mean ± SD. $p < 0.05$ indicated statistical significance and p = 0.000 was corrected to p < 0.001 (15).

Results

From May 2017 to December 2018, 71 ESRD patients were screened. Twenty-nine were eligible and 20 agreed to participate. Of the 20 healthy controls screened, all agreed to take part. All ESRD and healthy participants completed both CPEX and CLEX. One ESRD participant became fatigued during CLEX, briefly stopping twice to recover. No other participants in either group experienced any symptoms. Groups were well matched for age, gender and body mass index (table 1).

Table 1: Participant characteristics.

Participant characteristics	Healthy (n = 20)	ESRD (n = 20)	*P*
Age (yrs)	59 ± 10	59 ± 12	0.83
Weight (kg)	77 ± 16	74 ± 15	0.51
Height (cm)	175 ± 9	171 ± 10	0.31
BMI (kg/m^2)	25 ± 4	25 ± 4	0.92
Gender, n (male/female)	14/6	14/6	0.84
Ethnicity			
Black	1	5	N/a
Caucasian	19	13	N/a
Asian	0	2	N/a
Smoking status (n), (current/former/never)	0/0/20	3/3/14	N/a
Hemodialysis vintage (months)	N/a	41 ± 39	N/a
Central venous catheter (n, %)	N/a	2 (10)	N/a
Arterial venous fistula (n, %)	N/a	18 (90)	N/a
Comorbidities (n, %)			
Diabetes	0	4 (20)	N/a
Hypertension	6 (30)	12 (60)	N/a
Cerebral vascular disease	0	3 (15)	N/a
Coronary artery disease	0	7 (35)	N/a
Peripheral vascular disease	0	1 (5)	N/a
Chronic heart failure	0	2(10)	N/a

Carcinoma	0	3 (15)	N/a
Asthma	0	0	N/a
COPD	0	1 (5)	N/a
Hyperparathyroidism	0	5 (25)	N/a
Medication (n, %)			
Anti-hypertensives	5 (25)	16 (80)	N/a
Antiplatelet	1 (5)	3 (15)	N/a
Anticoagulants	0	8 (40)	N/a
Statins	1 (5)	8 (40)	N/a
Diuretics	0	5 (25)	N/a
Anti-Arrhythmic	0	1 (5)	N/a
Beta-blockers	0	11 (55)	N/a
Hypoglycemic agents	0	5 (5)	N/a

ESRD, end-stage renal disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ACE, angiotensin converting enzyme. Values expressed as absolute or mean ± SD.

Resting cardiopulmonary and arterial function

Left ventricular mass, end diastolic volume (LVEDV), A velocity and mean E/e' were higher in ESRD compared to healthy controls (table 2). FVC and FVC_1 were lower in ESRD but not indicative of restrictive or obstructive pulmonary disease. There was no difference between groups in augmentation index or pulse wave velocity.

Table 2: Resting cardiac, respiratory and vascular parameters

Echocardiogram	Healthy (n = 20)	ESRD (n = 20)	*P*
LVEF (%)	64 ± 6	63 ± 11	0.71
Stroke volume (ml)	62 ± 26	60 ± 20	0.81
LV mass (g)	185 ± 83	292 ± 102	0.01*
LV mass/BSA (g/m^2)	69 ± 51	148 ± 60	< 0.001*
LAESV (ml)	58 ± 23	69 ± 37	0.33
LVEDV (ml)	103 ± 40	117 ± 59	0.002*
LVEDV/BSA (g/m^2)	41 ± 25	62 ± 26	0.24
LVESV (ml)	39 ± 21	52 ± 36	0.39
LVESV/BSA	16 ± 11	24 ± 17	0.37
E-velocity (m/s)	0.77 ± 0.23	0.85 ± 0.31	0.52
Deceleration time (m/s)	226 ± 36	213 ± 40	0.43
A-velocity (m/s)	0.57 ± 0.14	0.90 ± 0.30	0.004*
E/a (m/s)	1.35 ± 0.61	1.08 ± 0.54	0.26
Mean E/e' (m/s)	6.48 ± 3.57	12.09 ± 6.50	0.02*
Spirometry			
FVC (L)	4.29 ± 0.95	3.44 ± 1	0.03*

% of predicted	108 ± 24	86 ± 23	0.02*
FEV_1 (L/sec)	3.22 ± 0.68	2.30 ± 0.88	0.02*
% of predicted	105 ± 21	81 ± 24	0.01*
FEV_1/FVC ratio	78 ± 5	75 ± 10	0.42
Brachial artery oscillometry			
Augmentation index	23.14 ± 10.34	28.75 ± 26.06	0.38
Pulse wave velocity (n/m)	8.6 ± 1.6	9.2 ± 1.6	0.19

ESRD, end-stage renal disease; LVEF, left ventricular ejection fraction; LV, left ventricular; BSA, body surface area; LAESV, left atrial end-systolic volume; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second. Values expressed as mean ± SD. *p < 0.05 between groups.

Cardio-pulmonary exercise test

At rest, breathing reserve was lower, and HR was higher in the ESRD group (table 3). At the anaerobic threshold and at peak exercise, VO_2, VCO_2, ventilation (VE), O_2 pulse, HR and work rate were lower in the ESRD group.

Table 3: Cardiopulmonary exercise test parameters.

CPEX parameters	Healthy (n = 20)	ESRD (n = 20)	*P* value
Rest			
VO_2 ($ml.kg^{-1}.min^{-1}$)	3.2 ± 0.9	3.3 ± 1.0	0.70
VCO_2 ($ml.kg^{-1}.min^{-1}$)	2.7 ± 7.3	3.1 ± 1.1	0.74
RER	0.88 ± 0.07	0.89 ± 0.10	0.87
VE (L/min)	9.6 ± 2.8	9.1 ± 2.6	0.59
O_2 pulse (VO_2/HR)	4.1 ± 1.2	3.3 ± 0.9	0.11
BR (%)	93 ± 3	90 ± 5	0.03*
RR (breaths/min)	16 ± 4	17 ± 5	0.61
PET CO_2	34 ± 3	37 ± 4	0.06*
HR (bpm)	64 ± 11	80 ± 15	0.002*
SBP (mmHg)	132 ± 18	138 ± 40	0.64
DBP (mmHg)	83 ± 13	81 ± 36	0.86
Anaerobic threshold			
VO_2 ($ml.kg^{-1}.min^{-1}$)	17.42 ± 7.00	9.15 ± 2.58	< 0.001*
VCO_2 ($ml.kg^{-1}.min^{-1}$)	17.56 ± 7.06	9.36 ± 2.82	< 0.001*
RER	1.00 ± 0.07	1.00 ± 0.06	0.76
VE (L/min)	38.9 ± 18.4	23.1 ± 6.8	0.002*
O_2 pulse (VO_2/HR)	12.5 ± 4.3	7.4 ± 1.9	0.001*
BR (%)	71 ± 13	74 ± 10	0.37
RR (breaths/min)	22 ± 5	22 ± 5	0.58

PET CO_2	42 ± 4	39 ± 4	0.07*
HR (bpm)	111 ± 21	94 ± 11	0.003*
SBP (mmHg)	159 ± 23	146 ± 34	0.24
DBP (mmHg)	79 ± 18	81 ± 31	0.82
WR (watts)	109 ± 62	39 ± 14	< 0.001*
Peak			
VO_2 ($ml.kg^{-1}.min^{-1}$)	24.6 ± 7.3	13.3 ± 2.7	< 0.001*
% predicted VO_2	90 ± 21%	47 ± 16%	< 0.001*
VCO_2 ($ml.kg^{-1}.min^{-1}$)	30.9 ± 7.1	15.00 ± 6.42	< 0.001*
RER	1.36 ± 0.20	1.26 ± 0.15	0.402
VE (L/min)	83.5 ± 18.1	45.3 ± 13.9	< 0.001*
O_2 pulse (VO_2/HR)	13.4 ± 4.3	8.9 ± 2.0	0.003*
BR (%)	42 ± 9	52 ± 19	0.10
RR (breaths/min)	34 ± 10	30.3 ± 7.4	0.27
PET CO_2	36 ± 6	36 ± 4	0.90
HR (bpm)	149 ± 15	113 ± 17	< 0.001*
SBP (mmHg)	182 ± 31	168 ± 40	0.24
DBP (mmHg)	97 ± 22	84 ± 28	0.29
WR (watts)	173 ± 66	70 ± 17	< 0.001*
OUES (L/min/log L/min)	1839 ± 825	1074 ± 183	< 0.001*
$\Delta VO_2/\Delta WR$ slope (ml/min/watt)	9.7 ± 1.4	9.2 ± 1.4	0.41
VE/VCO_2 slope	33 ± 8	32 ± 5	0.46

CPEX, cardiopulmonary exercise test; ESRD, end-stage renal disease; RER, respiratory exchange ratio; VE, minute ventilation; BR, breathing reserve; RR, respiratory rate; $PETCO_2$, end tidal carbon dioxide tension; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; WR, work rate; OUES, oxygen uptake efficiency slope. Values expressed as mean ± SD. *p < 0.05 between groups.

Constant load exercise test

Minute ventilation: Throughout exercise, mean VE was higher in healthy controls compared to ESRD (31.6 ± 2.0 *vs.* 20.0 ± 1.7 L/min, p < 0.001) (figure 1). When VE was expressed relative to peak VE attained during CPEX, the ESRD group ventilated at a higher percentage of peak (48 ± 3 *vs.* 39 ± 3%, p = 0.04). The relative increase in VE from rest was less in ESRD compared to healthy controls (124 ± 25 *vs.* 209 ± 26%, p = 0.02).

Heart rate: Mean HR was higher throughout exercise for healthy controls compared to ESRD although not statistically significant (95 ± 4 *vs.* 89 ± 4 bpm, p = 0.28) (figure 1). In contrast,

the ESRD group had a smaller relative increase in HR from rest than healthy controls (26 ± 5 *vs.* 59 ± 5%, $p < 0.001$). Additionally, the ESRD group exercised at a higher percentage of HR max (82 ± 2 *vs.* 64 ± 2%, $p < 0.001$).

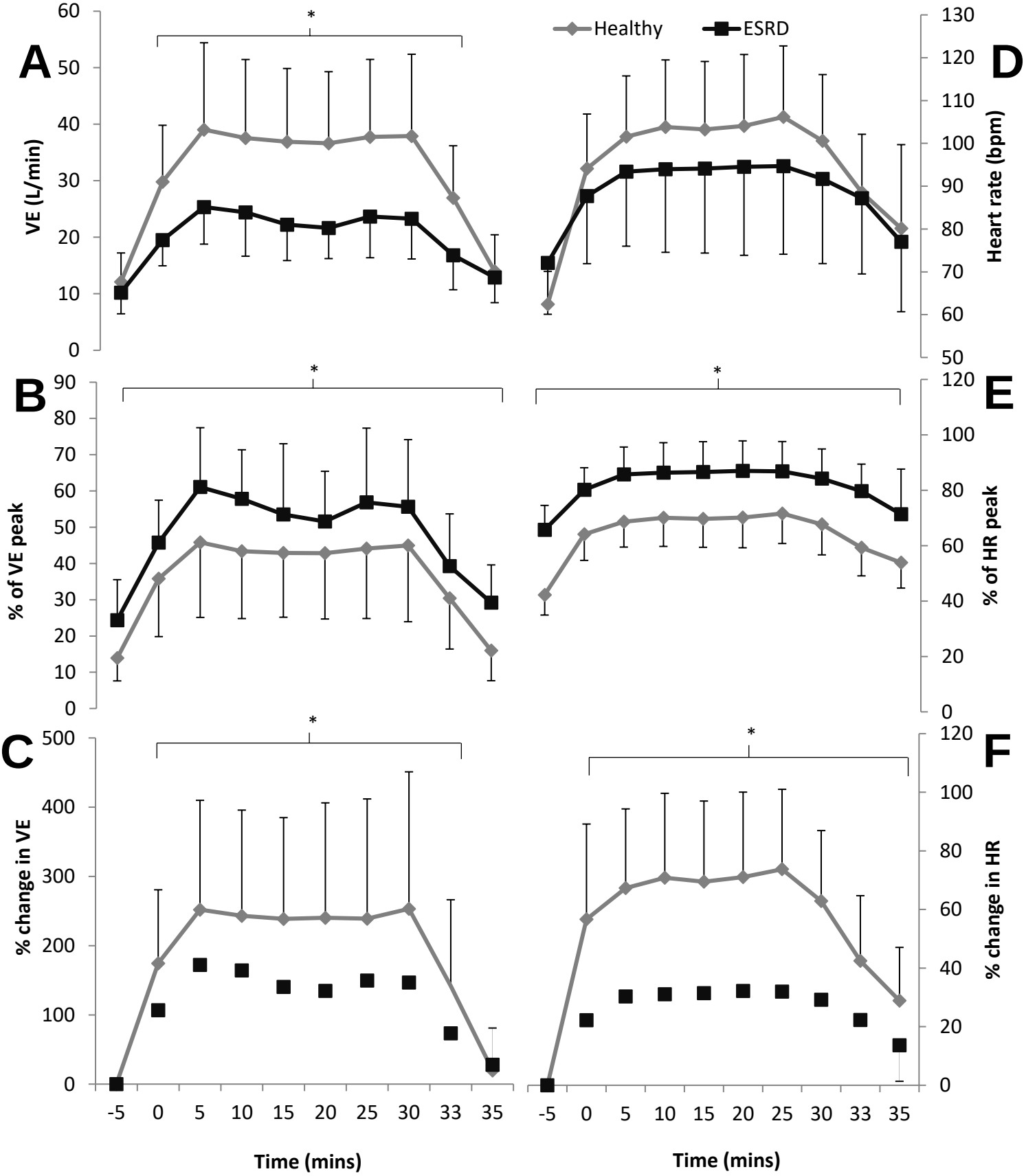
A
B
C
D
E
F
Healthy
ESRD
VE (L/min)
Heart rate (bpm)
% of VE peak
% of HR peak
% change in VE
% change in HR
*
Time (mins)
-5 0 5 10 15 20 25 30 33 35

Figure 1: ESRD, End-stage renal disease; VE, minute ventilation; HR, heart rate. VE (A), % of peak VE (B), % change in VE from rest to steady state (C), HR (D), % of peak HR (E) % change in HR from rest to steady state (F) during constant load exercise test in healthy and end-stage renal disease participants. -5 start of warm up. Zero minutes indicates start of CLEX. 30-33: 3-minute cool down. Values expressed as mean ± SD. *$p < 0.05$ between groups.

Arterial venous O_2 difference: There was no difference between groups in absolute (a-v) O_2 difference (figure 2). The relative change in (a-v) O_2 difference from rest was greater in healthy controls than in ESRD (74 ± 18 *vs.* 13 ± 18%, p = 0.03).

Stroke volume: Mean SV was greater during exercise for healthy controls compared to ESRD, but not significantly (124 ± 9 vs 111 ± 8 ml, p = 0.27) (figure 2). In contrast, the relative increase in SV from rest was greater in the ESRD group, again not significantly (50 ± 10 vs. 25 ± 11, p = 0.10).

Cardiac output: Mean CO was greater throughout exercise for healthy controls compared to ESRD (12.2 ± 0.8 vs 10.1 ± 0.7 L/min, p = 0.07), but did not reach statistical significance. There was no difference between the two groups in the relative increase from rest (104 ± 17 *vs.* 94 ± 15%, p = 0.65) (figure 2)

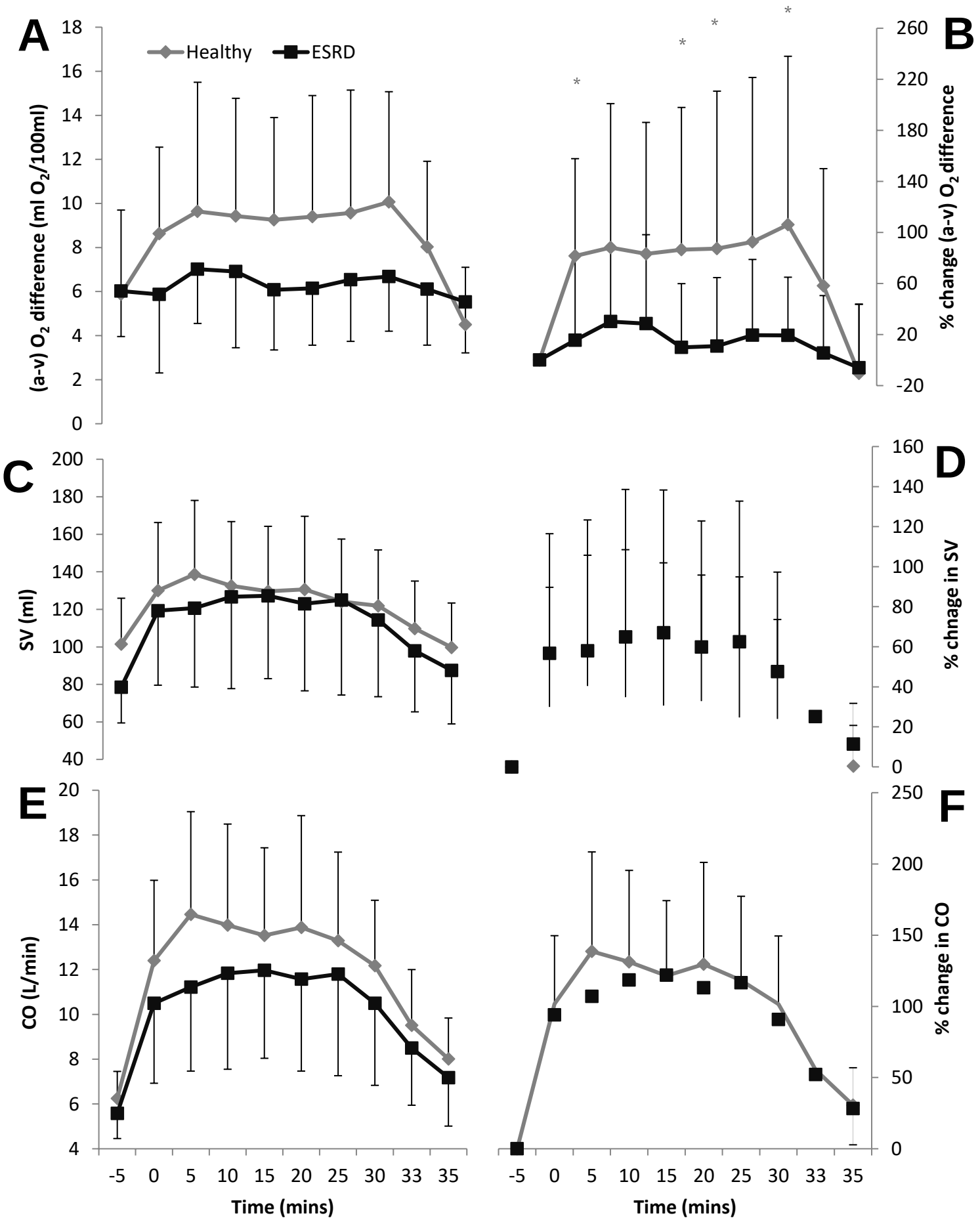
A
Healthy
ESRD
(a-v) O2 difference (ml O2/100ml)
B
% change (a-v) O2 difference
C
SV (ml)
D
% chnage in SV
E
CO (L/min)
F
% change in CO
Time (mins)
Time (mins)

Figure 2: ESRD, End-stage renal disease; (a-v) O_2 difference, arterial venous O_2 difference; SV, stroke volume, CO, cardiac output. (a-v) O_2 difference (A), % change in (a-v) O_2 difference (B), SV (C), % change in SV (D), CO (E), % change in CO (F) during CLEX between healthy and ESRD groups. -5 start of warm up. Zero minutes indicates start of CLEX. 30-33: 3-minute cool down. 33-35: 2-minute rest period. Values expressed as mean ± SD. *p < 0.05 between groups.

Ventilatory and hemodynamic parameters: Absolute, but not relative, VO_2 was lower throughout exercise in the ESRD group compared to healthy controls (table 4). Similarly, absolute, but not relative VCO_2 was higher. Mean respiratory exchange ratio was the same for both groups. Mean SBP was higher in the ESRD group compared to healthy controls whilst mean DBP and MAP were the same. TPR was higher in the ESRD group.

Table 4: Mean ventilatory and hemodynamic parameters during CLEX

	Healthy (n = 20)	ESRD (n = 20)	*P* value
VO_2 ($ml.kg^{-1}.min^{-1}$)	13.5 ± 3.7	8.1 ± 1.8	<0.001*
% of VO_2 peak	51.7 ± 14.1	62.1 ± 21.8	0.10
VCO_2 ($ml.kg^{-1}.min^{-1}$)	11.7 ± 3.2	7.6 ± 2.42	<0.001*
% of VCO_2 peak	39.3 ± 15.8	40.6 ± 12.7	0.80
RER	1.0 ± 0.1	1.0 ± 0.1	0.74
SBP (mmHg)	142.2 ± 16.9	158.0 ± 26.4	0.04*
DBP (mmHg)	86.2 ± 9.8	86.6 ± 18.9	0.93
MAP (mmHg)	105.0 ± 11.9	110.2 ± 20.2	0.34
TPR (mmHg)	828.9 ± 150.5	1011 ± 306.8	0.03*

Data as mean ± SD. -5 start of warm up. RER, respiratory exchange ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; TPR, total peripheral resistance. Values expressed as mean ± SD. *p < 0.05 between groups.

Discussion

By directly comparing the physiology of individuals with ESRD and age and gender-matched healthy controls, we identified previously unreported limitations during maximal and sub-maximal exercise. Most notably, in addition to the well-documented reduction in VO_2 peak in ESRD, we observed a marked impairment in heart rate, ventilation and oxygen extraction during sub-maximal constant load exercise. Our data suggest dysregulated cardiovascular, pulmonary and skeletal muscle physiology during sub-maximal and maximal exercise in patients with ESRD.

Resting physiological measures

Lung function was reduced at rest in ESRD participants, suggestive of chronic deconditioning. Although not extensively documented, these data add to the limited existing literature by directly comparing ESRD with age and gender-matched healthy controls (16, 17). Restrictive lung dysfunction is present in a third of individuals with ESRD (18), although was not evident in our data. Nevertheless, our findings indicate that ESRD results in decreased pulmonary function, possibly explained by physical deconditioning alone, or in combination with impaired ventilatory mechanics (19, 20). Echocardiography in our study indicated that LV mass and E/e' (LV filling pressure) were higher in the ESRD group. In combination, these findings suggest evolving LV hypertrophy and diastolic dysfunction in ESRD, which are well known predictors of exercise intolerance (21-23). Arterial compliance, assessed with augmentation index and pulse wave velocity, was similar between groups as previously reported between ESRD participants and hypertensive controls (24). Despite our comparator group consisting predominantly of normotensive controls, six participants were diagnosed with hypertension, which may explain this anomaly.

Cardiopulmonary exercise test

Reduced VO_2 peak is well documented in ESRD and is strongly predictive of mortality (1, 3, 24). In our study, VO_2 peak in the ESRD group was only 54% of that achieved by healthy controls. We can be confident that these values represent impaired function, as opposed to poor compliance with the maximal testing protocol, as indicated by an RER exceeding 1.25 in both groups. These data may reflect an increased mortality risk as previously indicated in

observational trials in ESRD (VO_2peak: < 17.5 ml.kg^{-1}.min^{-1}) (25, 26). Substantially decreased O_2 uptake efficiency (OUES) was also apparent in ESRD participants. Collectively these data confirm that our ESRD population were severely deconditioned, consistent with an advanced ESRD phenotype. Minute ventilation in ESRD participants was also only half that achieved by healthy controls during maximal exercise. In a previous study, this difference was not apparent in a cohort of CKD 3-4 patients (25), suggesting our finding may be unique to ESRD. These data indicate decreased respiratory reserve, likely due to both reduced respiratory drive and lower tidal volume during exercise, compared to healthy controls.

Below the anaerobic threshold, HR was higher in the ESRD group. Despite this, at VO_2 peak, HR max was reduced in ESRD participants, as has been previously reported (24, 25). Whilst the effect of beta-blockade in our ESRD group should be acknowledged, it is likely this was minimal given that only half of the ESRD group were prescribed beta-blockers, and resting HR was higher in the ESRD group. This suggests the difference between groups was not pharmacologically mediated, rather it reflects reduced HR reserve and chronotropic incompetence, as is common in cardiovascular disease, hypertension and heart failure (27). Chronotropic incompetence in ESRD is thought to be due to decreased catecholamine sensitivity resulting from impaired renal clearance of catecholamines and increased circulating angiotensin II (8, 28). Decreased O_2 pulse, a surrogate marker of stroke volume, was also evident at peak exercise and at the anerobic threshold in our study, potentially indicating impaired myocardial function during periods of increased metabolic demand. Therefore, it appears that cardiac output is impaired in ESRD by numerous mechanisms including chronotropic incompetence and diastolic dysfunction, thus limiting exercise capacity.

Constant load exercise test

In absolute terms, VE was significantly lower throughout CLEX in our ESRD cohort compared to healthy controls. The relative increase from rest was also lower but the ESRD group exercised at a higher percentage of VE max achieved during CPEX. These data suggest an inability to augment ventilation in response to exercise. This phenomenon has been described previously during exercise in small exploratory trials (6, 17). The precise mechanisms responsible for this are unknown, nevertheless, prevalence of pulmonary hypertension,

cardiomyopathy and decreased expression of pulmonary aquaporin five channels, risk fluid retention and pulmonary oedema in ESRD, which may limit mechanical ventilation through small airway dysfunction and pulmonary congestion (29). Decreased VE has also been documented during haemodialysis as a result of acute alkalosis from bicarbonate-based dialysate, which may persist during the post-dialytic period (30, 31). Acute alkalosis during the inter-dialytic period therefore may explain the abnormal VE response to exercise in our study, although data are not available to confirm this. Irrespective of the cause, our data and previous findings suggest that impaired pulmonary function greatly contributes to exercise intolerance in ESRD possibly as a result of ventilatory and gas exchange abnormalities.

Despite a significant difference in absolute VO_2 during CLEX between healthy controls and ESRD participants, there was no difference when this was expressed as a percentage of VO_2 peak achieved during CPEX i.e. CLEX was performed at the same relative intensity in both groups. However, a smaller percentage change in (a-v) O_2 difference was evident for the ESRD group, suggestive of impaired O_2 extraction. Subsequently, our data support reduced muscle energetic efficiency and O_2 extraction in ESRD. This decreased O_2 efficiency may contribute to exercise intolerance, limiting activities of daily living, and impacting on quality of life in ESRD (6, 32).

An attenuated HR response was evident during CLEX in our ESRD cohort compared to healthy controls. We observed a higher percentage of HR max, and a lower relative increase in HR in the ESRD cohort. Therefore, despite ESRD participants performing exercise at a higher relative HR, this represented a smaller relative increase from resting levels than in healthy controls. Chronotropic incompetence has been previously documented during sub-maximal exercise in ESRD participants, even in the presence of higher levels of circulating noradrenaline and adrenaline (8). This suggests that there may be a chronically decreased sensitivity to sympathetic hormones in ESRD, resulting in an inability to augment HR in response to increased metabolic demand.

In conjunction with a smaller relative increase HR in our ESRD cohort, the relative change in SV appeared to be greater, albeit not statistically significant. Cardiac output did not differ between groups, therefore, in response to greater metabolic demand in ESRD, CO may

depend on augmented SV in the absence of an increase in HR. This may be problematic in those with coexisting LV dysfunction evidenced in the current ESRD cohort by decreased O_2 pulse, and increased LV mass and diastolic filling pressures. When a rapid increase in CO is required, the inability to quickly increase either HR or SV will result in breathlessness, fatigue and exercise intolerance. These maladaptations, specifically decreased HR reserve, autonomic dysfunction, SV dependency and LV dysfunction, may explain reduced VO_2 peak during CPEX, and altered physiology during CLEX. These data improve our understanding of exercise intolerance, reduced quality of life and an inability to respond to hemodynamic challenges in ESRD.

Prior to exercise, blood pressure and total peripheral resistance were similar between groups. In contrast, during sub-maximal exercise, mean values for SBP and TPR were greater in the ESRD group. These data likely suggest endothelial dysfunction in our ESRD cohort during susatined sub-maximal exercise (6). Systemic vascular calcification and atherosclerosis likely contribute to this phenomenon. An inability to sufficiently induce arterial vasodilation likely further impedes O_2 utilisation at the tissue level, potentially limiting oxygen uptake in conjunction with cardiopulmonary dysregulation. These data support previous findings whereby arterial stiffness predicted reduced VO_2 peak (33, 34).

Limitations

It is likely that both the healthy and ESRD cohorts were too small to detect changes in this exploratory study for all the variables investigated, specifically haemodynamics during CLEX (CO and SV), which did not reach significance despite apparent differences. In addition, the ethnicity of our ESRD group differed from our predominantly Caucasian healthy controls but there is no evidence to support an effect of ethnicity on cardiopulmonary responses to exercise that would explain the current findings. We determined (a-v) O_2 difference indirectly using CO and VO_2, and used brachial artery oscillometry for the assessment of arterial stiffness which is not considered the gold standard method.

Conclusion

Maximal oxygen uptake was decreased in ESRD participants compared to healthy controls. Cardiovascular, pulmonary and skeletal muscle impairment was evident at rest and during maximal and sub-maximal exercise. Our exploratory study identified potential causes of exercise intolerance in ESRD, including compromised ventilatory function, chronotropic incompetence and impaired muscle O_2 extraction. These data provide new insights into exercise intolerance in ESRD and highlight potential therapeutic targets.

Author contributions

G. M., S. M. and E. J. H. designed the study; S. M. and K. C. was responsible for data collection; S. M. was responsible for data analysis; S. M. and G. M. drafted the manuscript; S. M., G. M., K. C., E. J. H., D. R., and N. K. revised the manuscript, and all authors approved the final version.

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